1 103. (Amended Twice) A method for directly identifying a non-endogenous compound as a compound having an activity selected from the group consisting of: inverse agonists, agonists, and partial agonists, to a non-endogenous, constitutively activated version of a known G protein-coupled receptor, said receptor comprising a transmembrane-6 region and an intracellular region, comprising the steps of:

(a) selecting a non-endogenous version of a known GPCR;

(b) confirming that the selected non-endogenous GPCR of step (a) is constitutively active;

(c) contacting a non-endogenous candidate compound with the non-endogenous, constitutively activated GPCR of step of (b); and

(d) determining, by measurement of the compound efficacy at said contacted receptor, whether said non-endogenous compound is an inverse agonist, an agonist, or a partial agonist to said receptor of step (b);

wherein said receptor of step (b) comprises the amino acid sequence of SEQ ID NO:449.

REMARKS

After entry of the present amendment, claims 101, 102, 103 and 105 will be pending in this application.

Claims 104 and 106-177 have been cancelled. Claim 103 has been amended to correct grammar, and to conform with Applicants' election set forth in their response of February 28, 2002. Thus, claim 103 now recites that the receptor of step (b) comprises SEQ ID NO:449. No new matter has been added.

The Office Action objects to the disclosure on the basis that it fails to state whether U.S. Application Ser. No. 09/170,496 is a continuation, continuation in part, or division of the 09/170.496 application. In response, Applicants note that the present application does not claim priority benefit of the 09/170,496 application, but nevertheless incorporates the content thereof by reference.

Applicants thank the Examiner for indicating the prior objection to the disclosure, and certain rejections under 35 U.S.C. §112 second paragraph and 35 U.S.C. §102(e) have been withdrawn.

Claims 101-104 stand rejected under 35 U.S.C. §102(b) for alleged anticipation by Herrick-Davis *et al.*, (Annals of the New York of Academy of Sciences 861:140-145, 1998, hereinafter "Herrick-Davis et al."). Applicants disagree with the assertions of the Office Action for the reasons presented in their prior response. Nevertheless, pursuant to the restriction requirement, Applicants have amended the claims to recite that the non-endogenous, constitutively activated version of the known G protein-coupled receptor comprise the amino acid sequence of SEQ ID NO:449. Inasmuch as Herrick-Davis et al. fails to teach or even suggest the amino acid sequence of SEQ ID NO:449, Herrick-Davis et al. cannot anticipate the claims. Accordingly, Applicants respectfully request the reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Claim 105 stands rejected under 35 U.S.C. § 103(a) for alleged unpatentability over Herrick-Davis *et al.* in view of Kohen *et al.* (J. Neurochem. 66:47-56, 1996, hereinafter "Kohen et al."). The Office Action admits that Herrick-Davis fails to teach the use of non-endogenous, constitutively activated forms of human 5-HT6 serotonin receptors. Nevertheless, the Office Action states that Kohen et al. teach the nucleotide and amino acid sequences of a human 5-HT6 receptor having a single amino acid difference from SEQ ID NO:449, and further asserts that it would have been obvious to:

> ... make the non-endogenous, constitutively activated forms of human 5-HT6 serotonin receptor from the cDNA sequence taught by Kohen et al. using the approach taught by Herrick Davis et al. and to include such mutants in the

method of Herrick-Davis et al.

Office Action at page 4.

Applicants respectfully request reconsideration of the rejection, as the Office Action has failed to provide any legally sufficient motivation to combine the references, and the combination proposed by the Office Action would still fail to teach or even suggest all the limitations of claims.

It is settled law that In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, the Office must provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that

> would **impel** one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

The only motivation asserted by the Office Action is the allegation on page 4 that:

> One would have been motivated to do so because serotonin receptors are an important class of G-protein coupled receptors, have important biological activity and are of potential interest to psychopharmacology as taught by Kohen et al. (page 47)

This is not the "motivating force" that would "impel" persons of ordinary skill to combine and modify the respective teachings of the cited references and achieve the claimed invention. The mere fact that serotonin receptors are important, and are of interest, simply is not the motivation required under the legal standard cited above. Indeed, every reference discloses information that is important and of interest.

Under 35 U.S.C. § 103, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). The Office Action has not pointed to any suggestion whatsoever in either reference to combine the respective teachings. Thus, it appears that the only motivation for combining the references is an impermissible hindsight reconstruction using knowledge gleaned only from Applicants' disclosure. *In re McLauglin*, 170 USPQ 209, 212 (CCPA 1971). Accordingly, the Office Action has failed to set forth a proper prima facie case of obviousness for this reason.

Moreover, even if the cited art were properly combinable (and it is not) the result still would not achieve Applicants' claimed invention. As discussed in Applicants' prior response, Herrick-Davis fails to teach or suggest ***methods*** for identifying a non-endogenous compound as an agonist or inverse agonist of a non-endogenous, constitutively active receptor, and the Kohen et al. reference fails to correct this

deficiency. Further, the Office Action points to no evidence that even when combined, those of skill in the art would have a reasonable expectation of success of obtaining a non-endogenous constitutively activated 5-HT6 receptor. It is only by reading Applicants' disclosure that such a expectation can be discerned.

In view of the preceding remarks, Applicants respectfully assert that the Office Action has failed to establish a *prima facie* case of obviousness for at least the reasons set forth above. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Applicants respectfully submit that the foregoing amendments place this application in condition for allowance. Applicants invite the Examiner to contact the undersigned at (215) 665-5548 to clarify any unresolved issues raised by this response.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants respectfully request early notification of the same.

Respectfully submitted,

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Date: January 10, 2003

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Attachments: "Version with markings to show changes made"

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 103 has been amended as shown below:

103. (Amended Twice) A method for directly identifying a non-endogenous compound as a compound having an activity selected from the group consisting of: inverse agonists, agonists, and partial agonists, to a non-endogenous, constitutively activated version of a known G protein-coupled receptor, said receptor comprising a transmembrane-6 region and an intracellular region, comprising the steps of:

(d) selecting a non-endogenous version of a known GPCR;

(e) confirming that the selected non-endogenous GPCR of step (a) is constitutively active;

(f) contacting a non-endogenous candidate compound with the non-endogenous, constitutively activated GPCR of step of (b); and

(d) determining, by measurement of the compound efficacy at said contacted receptor, whether said non-endogenous compound is an inverse agonist, an agonist, or a partial agonist to said receptor of step (b);

wherein said receptor of step (b) comprises the amino acid sequence of SEQ ID NO:449.

Claims 104 and 106-177 have been cancelled.